REMARKS

Status of the Claims.

Claims 8-22, and 27-36 are pending with entry of this amendment, claims 1-7, 23-26, and 37-76 being cancelled and no claims being added herein. Claims 9, 11, 12, 27, and 29 are amended herein. These amendments introduce no new matter. Support is replete throughout the specification and, particularly in the claims as filed. It is noted that these amendments do not alter the scope of the claimed invention..

Election/Restriction.

Pursuant to a restriction requirement made final, Applicants cancel claims 1-7, 23-26, and 37-76 with entry of this amendment. Please note, however, that Applicants reserve the right to file subsequent applications claiming the canceled subject matter and the claim cancellations should not be construed as abandonment or agreement with the Examiner's position in the Office Action.

Objection to the Specification:

The specification was objected to because it allegedly contains an embedded hyperlink and/or other form of browser-executable code at several places, for example, on page 72 (line 12) and page 73 (line 31). The Examiner requested amendment of the specification to eliminate this alleged browser code.

The specification has been amended herein on pages 12, 72, and 73 to recite "www.ncbi.nlm.nih.gov", "www.ri.bbsrc.ac.uk", and "www.ncbi.nlm.nih.gov".

M.P.E.P. §7.29.03 expressly states:

> Examiners must review patent applications to make certain that hyperlinks and other forms of browser-executable code, especially commercial site URLs, are not included in a patent application. Examples of a hyperlink or a browser-executable code are a URL placed **between these symbols "< >" and http:// followed by a URL address**. When a patent application with embedded hyperlinks and/or other forms of browser-executable code issues as a patent (or is published as a patent application publication) and the patent document is placed on the USPTO web page, when the patent document is retrieved and viewed via a web browser, the URL is interpreted as a valid HTML code and it becomes a live web link. When a user clicks on the link with a mouse, the user will be transferred to another web page identified by the URL, if it exists, which could be a commercial web site. USPTO policy does not permit the USPTO to link to any commercial sites since the USPTO

> exercises no control over the organization, views or accuracy of the information contained on these outside sites. [emphasis added]

The amended paragraphs include neither the "<>" symbols nor "http://". Accordingly, the amended text is not a hyperlink or browser executable code and the Examiner's objection is obviated.

Information Disclosure Statement.

Applicants note that the Examiner did not consider references 2-6 of the Information Disclosure Statement alleging that these references are Genbank sequence listings and Applicants did not provide any statement as to how these references are relevant to the instant application.

Applicants expressly request again that the Examiner consider these references and properly make them of record in the prosecution. To Applicants knowledge there is no requirement in the M.P.E.P. stating that Applicants must provide a statement as to the relevance of references provided in a PTO form 1449. Moreover, Applicants note that the other cited references were considered and made of record without a statement of relevance.

If the Examiner persists in refusing to properly consider these references, he is invited by the Applicants to provide statutory authority, rule, or M.P.E.P. section supporting such inaction. Absent such, it is Applicants position that these references were properly provided to the Patent Office and deemed by the Examiner to be of no relevance to the prosecution.

Claim Objections.

The Examiner objected to the word "as" before neo in claim 11. Claim 11 is amended to correct this typographical error.

Claims 8-22 and 27-36 were objected to because the allegedly have not used the term "Socs2" or "SOCS2" consistently. In view of the amendments made herein, the term "Socs2" is used with reference to the gene, while the term "SOCS2" is used with reference to the protein encoded by the Socs2 gene. The usage is consistent and further change is necessary.

Claim 29 was objected to because the word "wherein" was repeated in line 1. Claim 29 is amended herein obviating this objection.

35 U.S.C. §101:

Claims 12-22 were rejected under 35 U.S.C. §101 because the claimed invention was allegedly directed to non-statutory subject matter because the phrase "knockout mammal" allegedly

encompasses a human. Per the Examiner's recommendation, claim 12 is amended herein to recite ""a knockout non-human mammal" thereby obviating this rejection.

35 U.S.C. §112, Second Paragraph.

Claims 8-22 and 27-36 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite as described below.

A) High growth phenotype.

Claims 8 and 13 were allegedly vague and indefinite because it is allegedly unclear what is meant by the term "a high growth phenotype". Applicants traverse.

The Examiner is reminded that a claim is deemed definite if "... read in light of the specification [it] reasonably apprise[s] those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits." *Hybritech Inc. v Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986) *cert. denied* 480 U.S. 947 (1987) *citing Shatterproof Glass*, 225 USPQ 634, 641 (Fed. Cir. 1985).

In the instant case, the term high growth phenotype or "hg phenotype" is a term of art well known to those of skill in the art. It is understood to refer to a phenotype in weight gain and mature body size is increased. Thus, for example, Horvat and Medrano (1995) *Genetics,* 139: 1737-1748 (attached as Exhibit A) expressly states

> The high growth locus (hg) is a major locus that increases weight gain and mature body size of mice by 30-50% . . .

The terms high growth phenotype or hg phenotype thus clearly apprise those skilled in the art of the utilization and scope of the invention and are as precise as the subject matter permits. Accordingly the rejection of claims 8 and 13 under 35 U.S.C. §112, second paragraph, on these grounds should be withdrawn.

B) Antecedent basis.

The Examiner alleged that claim 9 recites the limitation "said Socs2 gene" in line 3 and there is insufficient antecedent basis for this limitation in the claim because it is unclear as to which

Socs2 gene the term is referring. Applicants have amended claim 9 to that both occurrences recite "said Socs2 gene" and clearly refer to claim 8 thereby obviating this rejection.

C) "Said mammal comprising cells containing a . . ."

The Examiner rejected claims 12, 30 and 31 because it is allegedly unclear as to what is meant by the term "said mammal comprising cells containing a . . . ". Applicants traverse.

Applicants respectfully submit that the language is clear on its face. It refers to an animal having cells that contain a disrupted (*i.e.* knocked out) *Socs2* gene. If the Examiner maintains this rejection he is invited to offer language that he believes is more clear.

D) "Disruption comprising an expression cassette".

Claim 17 was rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite because it is allegedly unclear what is meant by "disruption comprising an expression cassette". Applicants traverse. The specification, at page 29, lines 23-30 states:

> The phrases "disruption of the gene" and "gene disruption" refer to insertion of a nucleic acid sequence into one region of the native DNA sequence (usually one or more exons) and/or the promoter region of a gene so as to decrease or prevent expression of that gene in the cell as compared to the wild-type or naturally occurring sequence of the gene. By way of example, a nucleic acid construct can be prepared containing a DNA sequence encoding an antibiotic resistance gene which is inserted into the DNA sequence that is complementary to the DNA sequence (promoter and/or coding region) to be disrupted.

One of ordinary skill in the art would thus readily understand that "a disruption comprising an expression cassette" refers to an insertion of an expression cassette into a region of the, in this case, Socs2 gene. The phrase thus clearly apprises those skilled in the art of the utilization and scope of the invention and is as precise as the subject matter permits. Accordingly the rejection of claim 17 under 35 U.S.C. §112, second paragraph, on these grounds should be withdrawn.

35 U.S.C. §112, First Paragraph, description requirment.

Claims 11-22 and 27-36 were rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to

enable one skilled in the art to which it pertains, or with which it is most nearly connected to make and/or use the invention. It is noted that while paragraph 12 of the Office Action contains language typically used with respect to "make and use enablement" rather than "description requirement" Applicants note that the rest of the Examiner's rejection refers to the description requirement and applicants respond below accordingly.

The Examiner, argues that the art of "knockout animals is highly unpredictable and consequently the structure of the animals and the phenotype of the genus of animals encompassed by the broad claim cannot be predicted. The Examiner cites Wood (2000) *Comparative Medicine* 50(1): 12-15 as allegedly teaching that the phenotype of a transgenic mouse cannot be predicted. The Examiner also alleged "even if one has made a transgenic mouse of a gene using certain construct, the phenotype of other species of knockout or transgenic animals cannot be predicted. In support of this Examiner cites a paper by Hammer *et al.* (1990) Cell 63: 1099-1112 in which mice and rats expressing human HLA-b27 and beta-2 microglobulin showed different phenotypes. Applicants traverse.

The Examiner is reminded that "[t]he written description requirement **does not require the applicant 'to describe exactly the subject matter claimed**, [instead] the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed. [emphasis added] '" *Union Oil Co. v Atlantic Richfield et al.* 208 F.3d 989 (Fed. Cir. 2000) *citing In re Gosteli*, 872 F.2d 1008, 1012, 10 U.S.P.Q.2D (BNA) 1614, 1618 (Fed. Cir. 1989).

In the present case, claim 12 is directed to:

> 12. A knockout non-human mammal, said mammal comprising cells containing a recombinantly introduced disruption in a Socs2 gene, wherein said disruption results in said knockout mammal exhibiting decreased levels of SOCS2 protein as compared to a wild-type mammal.

While claim 27 is directed to:

> 27. A **knockout rodent** comprising a recombinantly introduced disruption in an endogenous SOCS2 gene (*Socs2*) wherein said disruption results in said knockout rodent exhibiting decreased levels of SOCS2 protein as compared to a wild-type rodent.

Applicants have produced knockout mice having a disruption in the *Socs2* gene and showing the high growth phenotype. Having demonstrated that Socs2 knockout mammals are viable

and exhibit the hg phenotype, one of ordinary skill in the art would appreciate that Applicants are in possession of the claims invention.

With respect to the Examiner's argument that the art is unpredictable and consequently Applicants have failed to show possession of the claimed genus, it is noted that the Wood article cited by the Examiner allegedly teaches that phenotypes cannot *a priori* be predicted. **In the instant case, Applicants have produced the claimed knockout, and provided a detailed phenotypic analysis.** Given that the knockout has been produced, shown to be viable, and shown to have the recited phenotype, the art is no longer unpredictable with respect to *Socs2* knockouts and the genus is properly and fully described.

Applicants also note that Cameron (1997) Mol. Biotechnology, 7: 253-265, cited by the Examiner **described challenges pertaining to the expression of heterologous genes in various hosts, not to the production of knockouts.**

The expression of a heterologous gene in a host animal entails far more difficulties (*e.g.* stable integration, induction of transcription, post-translational modification, timing of transcription/translation, tissue and/or cell specificities and the like) then the simple disruption of an **endogenous** gene as is contemplated by the present invention. Because Cameron pertains to the expression of heterologous genes in a host not to the inhibition/disruption of endogenous genes, it **does not** properly support the Examiner's argument that Applicants have failed to disclose the claimed genus.

With respect to the Korach *et al.* patent (US 5,650,550) cited by the Examiner, Applicants agree that one of skill might not have predicted that such an animal would have the resulting phenotype or even be viable. However, having shown that mice having the disrupted gene are viable, Applicants believe that it is generally predictable that other mammals having the same gene knocked out will also be viable and show a similar phenotype. Thus, Korach *et al.* **does not** negative Applicant's assertion or support the Examiner's argument that Applicants have failed to described the claimed genus. In view of these considerations, Applicant believe the Examiner has failed to make his *prima facie* case and the rejection of claims -22 and 27-36 under 35 U.S.C. §112 on these grounds should be withdrawn.

35 U.S.C. §112, First Paragraph, "make and use" enablement.

Claims 8-22, and 27-36 were rejected under 35 U.S.C. §112, first paragraph, because "the specification, while allegedly being enabling for a homozygous knockout mouse where both the alleles of the endogenous Socs2 gene in the genome of the mouse have been disrupted by inserting an expression cassette and wherein the knockout mouse is characterized by a large size and increased body weight and lack of functional Socs2 protein and a method of producing the knockout mouse does not reasonably provide enablement of the other recited embodiments. Applicants traverse.

Applicants first note that the Examiner stipulates that the homozygous knockout as recited above, is enabled. One of sill will readily appreciate that using such a homozygous animal in an outcross (*e.g.*, by out crossing with wild type) heterozygous animals can also readily be produced.

Applicants also note that the Examiner inappropriately confuses making a knockout animal with making a transgenic animal. In a knockout animal all that needs to occur is disruption of expression of the endogenous gene (*i.e.*, *Socs2* in the present case). In contrast, transgenic animals as described by Cameron (cited by the Examiner) require successful integration, induction, transcription, and translation of a heterologous protein. This is far more complicated than the simple disruption of expression of an endogenous gene. The Examiner's comments regarding Cameron simply do not bear on the production of knockout animals.

The Examiner's comments regarding the art of culturing and maintaining ES cells also does not negative the presently claimed invention. One of ordinary skill in the art would readily appreciate that the Socs2 gene can be knocked out in particular cells (including somatic cells) and then Socs2 knockout animals can be produced by nuclear transfer techniques with, at most, routine experimentation..

The production of viable cloned mammals following nuclear transfer of cultured somatic cells has been reported for a wide variety of species including, but not limited to frogs (McKinnell (1962) *J. Hered.* 53, 199–207), calves (Kato *et al.* (1998) *Science* 262: 2095–2098), sheep (Campbell *et al.* (1996) *Nature* 380: 64–66), mice (Wakayamaand Yanagimachi (1999) *Nat. Genet.* 22: 127–128), goats (Baguisi *et al.* (1999) *Nat. Biotechnol.* 17: 456–461), monkeys (Meng *et al.* (1997) *Biol. Reprod.* 57: 454–459), and pigs (Bishop *et al.* (2000) *Nature Biotechnology* 18: 1055-1059). Nuclear transfer methods have also been used to produce clones of transgenic animals. Thus, for example, the production of transgenic goats carrying the human antithrobin III gene by somatic cell

nuclear transfer has been reported (Baguisi *et al.* (1999) *Nature Biotechnology* 17: 456-461). Thus, knockout animals of this invention can be made even without ES cells.

The Examiner is also reminded that to be enabling under §112, first paragraph, a patent must contain a description that enables one skilled in the art to make and use the claimed invention . That some experimentation is necessary does not constitute a lack of enablement; the amount of experimentation, however, must not be unduly extensive.

Whether undue experimentation is required by one skilled in the art is typically determined by reference to eight factors considered relevant to the inquiry (1) the nature of the invention; (2) the breadth of the claims; (3) unpredictability of the art; (4) the state of the prior art; (5) the presence of working examples; (6) amount of guidance in the specification; (7) the level of skill in the art; and (8) the quantity of experimentation necessary. In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988) *citing Ex parte Forman Inc.*, 230 USPQ 546 (BPIA 1986).

In the instant case, the nature of the invention (Factor 1) is relatively straightforward pertaining to animals having a disruption in a particular designated gene (Socs2). The claims are not overly broad (Factor 2), independent claim 12 being directed only to knockout non-human mammals comprising cells containing a recombinantly introduced disruption in a Socs2 gene, and independent claim 27 being directed to a **knockout rodent** comprising a recombinantly introduced disruption in an endogenous *Socs2* gene. Having demonstrated that *Socs2* knockout animals are viable and show a high growth phenotype, the art is highly predictable (Factor 3). The prior art in the area is well developed (Factor 4). Many knockout animals have been produced and the methods of such production are routine. Working examples (Factor 5) are provided. Considerable guidance (Factor6) is provided in the example showing how to knockout a *Socs2* gene. The level of skill in the art (Factor 7) is high, typically being Ph.D. The quantity of experimentation is not great and is routine in nature Applicants having demonstrated how to knockout a Socs2 gene, having demonstrated that Socs2 knockouts are viable, and having demonstrated that such knockouts have a high growth phenotype.

All of the Wands factors weigh in favor of no undue experimentation. Thus, in view of the foregoing comments, Applicants believe the Examiner has failed to make his prima facie case and the rejection of claims 8-22, and 27-36 under 35 U.S.C. §112, first paragraph, should be withdrawn.

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is

respectfully requested. Should the Examiner seek to maintain the rejections or make new rejections, Applicants request a telephone interview with the Examiner and the Examiner's supervisor.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 769-3513.

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document2